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Is there a socioeconomic variation in survival from renal tumours in children and young people resident in northern England (1968 – 2012)?

Running title: Socioeconomic variation in renal tumour survival

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ABBREVIATIONS

CNS	central nervous system
GP	General Practitioner
ICCC-3	International Classification of Childhood Cancers, Third edition
IQR	inter-quartile range
NHS	National Health Service
NRYPMDR	Northern Region Young Persons' Malignant Disease Registry
NWRT	Non-Wilms renal tumour
RVI	Royal Victoria Infirmary
SES	socioeconomic status
SIOP	International Society of Paediatric Oncology
UK	United Kingdom
UKCCSG	United Kingdom Children's Cancer Study Group
WT	Wilms tumour

ABSTRACT

Background.
Despite strong evidence of a social gradient in cancer survival among UK adults, studies in children and young people remain inconclusive and have not included renal tumours. This study investigated the relationship between socioeconomic status and survival from renal tumours among children and young people.

Procedure.
Kaplan-Meier estimation and Cox regression were used to analyse survival for all 209 renal tumours in children and young people (0-24 years) diagnosed 1968-2012 and registered by a specialist population-based registry. Sociodemographic and clinicopathologic variables, including paternal occupation at birth, were also analysed.

Results.
No significant disparity in overall renal tumour and Wilms tumour (WT) survival was observed according to paternal social class [$p = 0.988$ and 0.808, respectively]. The strongest predictor of survival was stage, with late stage (III-IV) disease having a 4-fold higher risk of death compared to early stage (I-II) disease [$p < 0.001$]. Similarly, high mortality-risk was seen for late stage WT in children aged 0-14 years (Hazard Ratio = 6.37; 95% CI = 2.60-15.59).

Conclusions.
This study did not detect a significant social gradient in renal tumour survival. The identification of tumour stage as a strong predictor of survival irrespective of age, necessitates the development of appropriate public health interventions that target early diagnosis and treatment.

INTRODUCTION

Although survival has improved over the past four decades [1], cancer remains the leading cause of death for children (0-14 years) and young people (15-24 years) in the UK [2]. While rare in these age groups, renal tumours are an important heterogeneous group of cancers, representing 4-7% of new cases in children (0-14 years) and <1% of cases in young people (15-24 years) [3]. For several decades renal tumours have had one of the best prognostic outcomes among childhood cancers [3]. Population-based data from Europe and North America estimate 5-year survival to be > 85% for Wilms tumour (WT) and > 80% for all renal tumours [4,5]. Although 5-year survival from childhood renal tumours in the UK has improved over the past 40 years from 60% to 90% [6], with similar findings for northern England [7], survival rates continue to lag behind those of other European countries [4]. This puts childhood renal tumours at the forefront of the UK government's National Cancer Strategy to identify modifiable prognostic factors for all childhood cancers [8]. Additionally, very few studies have attempted to estimate renal tumour survival in young people, and recent European data have shown that unlike childhood renal tumours, survival has not improved significantly in young people aged 15-24 years with renal tumours [9].

While studies have highlighted socioeconomic status (SES) as a strong predictor of survival from adult malignancies in developed countries including England [10,11,12], few studies have investigated the role of social deprivation in cancer survival among children and young people [13,14,15], with none examining renal tumours. An older study of fathers' occupations had found an unexpected association between higher paternal social class and greater chance of the child dying from a malignancy [16].

Northern England has persistently had poorer health than the rest of England and continues to experience a widening health gap [17]. Limited information is available regarding social determinants of cancer survival among children and young people resident in northern England. Findings from the few studies that have investigated this phenomenon have also tended to be contradictory. While studies using individual-level measures of SES have identified a significant association between social class and survival from childhood cancers such as leukaemia [13], those using area-level measures have been less consistent [14,18,19].

This study investigated whether survival from renal tumours in children and young people resident in northern England varied according to socioeconomic status as assessed by paternal occupation at birth.

METHODS

The study population constituted all cases of malignant renal tumours in children (defined as ages 0-14 years) and young people (defined as aged 15-24 years), diagnosed 1968-2012 and registered on the Northern Region Young Persons' Malignant Disease Registry (NRYPMDR). The registry's study area covers the northern region of England and is located in the Newcastle upon Tyne Hospitals NHS Foundation Trust, a designated UKCCSG centre which also serves as the regional specialist centre for the treatment and management of adolescent cancers with a case ascertainment of 98% [20]. All cases are manually followed up through annual contact with responsible clinicians to determine patients' current vital status and with GPs if patients have been discharged from long-term hospital clinics. This has resulted in < 1% of cases being lost to follow up [7]. Malignancies in the registry are grouped according to the International Classification of Childhood Cancers, Third edition (ICCC-3) [9].

Demographic information (age at diagnosis, gender) and details of diagnosis (year of diagnosis, tumour stage, histological subtype), are documented by the registry. Whenever possible, a copy of the birth certificate – which records paternal occupation – is also obtained.

Paternal occupation – a reliable proxy measure of SES [13, 21] – was coded using the revised 1990 Standard Occupational Classification and used to assign paternal social class at the time of the study participant's birth, classified as: I – Professional; II – Managerial; IIIN – Skilled non-manual; IIIM – Skilled manual; IV – Semi-skilled; V- unskilled. Class I was considered to be the most affluent and class V the most deprived. To enable ease of analysis and comparison with other similar studies, these social classes were collapsed into the following 3 categories: Class I/II – Professional/Managerial; Class IIIN/M – Skilled non-manual/manual; Class IV/V – Semi-skilled/unskilled. A subset of study cases without documented paternal

occupation or for whom no appropriate social class could be coded was created. Renal tumours were classified according to histological subtype based on ICCC-3 and further collapsed into 2 categories: Wilms Tumours (WT) and Non-Wilms renal tumours (NWRTs). Age at diagnosis was categorized as: 0-1, 2-4, 5-14 and 15-24 and year of diagnosis for all renal tumours was classified as 1968-1977, 1978-1987, 1988-1997, 1998-2007 and 2008-2012, with further analysis for WT cases according to clinical trial dates. The trial dates used for WT cases aged 0-14 years were based on clinical trials open in the UK during our study period [22-27]. The trial periods followed were: 1968-1979 (MRC-1 and MRC-2 trials), 1980-2001 (UKW1, UKW2 and UKW3 were grouped together due to small numbers and overlapping dates), and 2002-2012 (SIOP WT trial). Registry information on tumour stage is routinely obtained from histopathology reports and/or consultant notes and was categorized as early stage disease (stage I-II), late stage disease (stage III-IV), and bilateral disease for WT based on current SIOP/UKCCG staging criteria [3]. The most recent estimate for central re-examination of biopsy specimens is noted to be 78% [20].

Statistical Analysis

All study covariates were treated as categorical variables, except age and year of diagnosis, which were also considered as continuous variables. Mann Whitney and Kruskal Wallis tests were used respectively to investigate the differences in median age at diagnosis between the sexes and across calendar periods, while Chi-square test was used to analyse associations between SES and covariates. Survival time was calculated as time in years from date of diagnosis to death from any cause or the last day of availability of survival information in the NRYPMDR. Study cases who were still alive were right censored from 31 December 2015. The Kaplan-Meier method was used to estimate one-, five- and ten-year survival rates according to the covariates and survival differences between groups tested via the log-rank

method. Hazard ratios (HRs) with 95% confidence intervals (CI) were obtained using the univariate Cox proportional hazards to assess effect of individual covariates on survival.

Multivariate Cox regression was used to examine effect of social class on survival while controlling for potential confounding from demographic and clinicopathologic factors. Due to the relatively few cases of NWRTs, bilateral WT and young people (15-24 years) with renal malignancies within the study population, these parameters were excluded from the final Cox modelling and instead a subgroup survival analysis of all children (0-14 years) with WT was performed using multivariate Cox regression to adjust for relevant clinical and epidemiological covariates. Interactions were tested within the Cox regression framework. The likelihood ratio test was used in the assessment of nesting effects. A significance level of 0.05 was chosen for all tests. The Schoenfeld residuals were used to investigate the validity of the proportional hazards assumption for the Cox regression models and the global score test of proportional hazards based on the scaled Schoenfeld residual was used for all significant covariates. All analyses were performed using STATA version 14.0.

RESULTS

Descriptive Characteristics of Study Population

209 renal tumours were diagnosed during the study period. The sociodemographic and clinicopathologic characteristics of the study population are summarized in Table 1. Children with WT accounted for 78% of the study population and over 70% of cases were diagnosed before 5 years of age with children aged 2-4 years constituting the modal age group while less than 10% of tumours occurred in young people (Table 1). Age at diagnosis ranged from 0-24 years, with a median age of 3 years and interquartile range (IQR) of 5 years. There was no significant sex difference in age at diagnosis ($p = 0.998$).

The study population consisted of 116 females and 93 males. While this sex distribution was maintained for children aged 0-14 years (male: female = 0.8), the proportion of males was slightly higher than females among young people aged 15-24 years (male: female = 1.1). Information on paternal social class was available for 183 cases. The modal social class was IIIn/m and there was no association between SES and tumour stage ($p = 0.502$) or histological subtype ($p = 0.958$).

WT was the most commonly diagnosed renal tumour (85% of cases) (Table 1). This was similar across all diagnostic periods, during which there was no significant change in the proportion of WT and NWRTs cases ($p= 0.267$). A higher proportion of WT and NWRTs cases were noted to present with early stage tumours than with late stage disease (53% vs 47% and 80% vs 20% respectively, $p = 0.019$). WT was mostly diagnosed before age 15 years – accounting for 162 cases with a median age at diagnosis of 3 years (IQR= 3 years). Conversely, the majority of NWRTs were seen in young people (55% of cases) with a median age of 18 years (IQR = 19 years). Overall, diagnosis with NWRTs was predominantly among males (male: female = 1.1),

becoming more noticeable in young people (male: female = 1.4). By contrast, children diagnosed with NWRTs or WT were mostly female (male: female = 0.8). Of the 209 study cases, 59 had died by the end of the follow up period (Table 1).

Kaplan-Meier Survival Estimates and Univariate Cox Regression Analysis

The crude survival rates and unadjusted hazard ratios (HR) on univariate analysis according to sociodemographic and clinicopathologic factors for all study cases are outlined in Table 2. Overall survival from renal tumours was 86% at 1-year after diagnosis, falling to approximately 74% from 5-years onward. The median duration of survival for all study cases was 17 years (IQR = 26 years), being longer for WT cases (Median survival = 19 years; IQR = 25 years) than for NWRTs (median survival = 6 years; IQR = 16 years).

There was no significant disparity in renal tumour survival according to paternal social class at birth **(**Figure 1). Survival rates remained similar for all social classes at all time points, with a 17-18% increased risk of mortality in the lower social classes compared to the most affluent socioeconomic group, although this was not found to be statistically significant (Table 2). Survival from early stage tumours and WT was consistently better across all social classes compared to late stage tumours and NWRTs respectively.

Little difference was seen in survival among the three childhood age groups. In contrast, young people with renal tumours were found to have a significantly higher risk of dying compared to the youngest age group (crude HR = 4.43; 95% CI = 1.88, 10.45). The study period saw a progressive improvement in renal tumour survival except during the last 2 periods (1998-2007 and 2008-2012) in which survival was slightly higher in 1998-2007 period compared to 2008-2012 (Table 2), possibly due to shorter duration (with fewer cases) of the latter period. There

was substantial disparity in survival from renal malignancies depending on tumour stage at diagnosis ($p < 0.001$; Figure 2). Study cases with early stage tumours had a significantly higher survival rate than those with late stage and bilateral WT (Table 2). Diagnosis with late stage tumour carried a three-and-a-half-fold increased risk of death compared to early stage tumours ($p < 0.001$), while bilateral WT was associated with an approximately three-fold higher risk of dying compared to early stage tumours ($p = 0.040$). Similarly, survival was significantly worse for those diagnosed with NWRTs compared to WT, with the disparity becoming especially pronounced from 5-years post-diagnosis onward (Table 2). The risk of dying was twice as high for cases diagnosed with NWRTs compared to WT ($p = 0.026$).

Subgroup Analysis – Multivariate Cox Modelling for Children (0-14 years) with WT

Prior to multivariate Cox modelling, Kaplan-Meier survival estimation and univariate Cox regression were carried out for all childhood WT cases aged 0-14 years (Supplemental Table S1, Supplemental Table S2, Supplemental Table S3). No significant association was noted between paternal social class and other study covariates (Supplemental Table S2), while presentation with late stage WT was observed to increase with age ($p = 0.001$, Supplemental Table S2). Cox regression modelling showed trial period and tumour stage at diagnosis to be significant in the final model (Table 3) and did not abrogate the proportional hazards assumption (Global test $\chi^2 = 4.00$, df = 8; $p = 0.857$). Children with late stage WT had a six-fold higher risk of dying compared to children with early stage disease and there was a significant reduction in mortality risk for patients treated during the latter trial periods compared to the MRC 1 and 2 trials which ran from 1968-1979 (Table 3). Marked improvement was observed in 5-year survival between the first and last calendar periods (i.e. 1968-1977 and 2008-2012) from 65% to 94% (Supplemental Table S3). There was little to no variation in childhood WT survival according to paternal social class at birth ($p = 0.808$), and the most

deprived socioeconomic groups were not found to be at a significantly higher risk of dying compared to the more affluent, even after adjusting for significant covariates (Table 3). Interactions were considered but not included in the final model due to small case numbers and missing data particularly for tumour stage and SES. However, conducting a subgroup analysis by trial period revealed no significant effects for SES over the trial periods ($p > 0.05$).

DISCUSSION

This is the first population-based study to exclusively examine the role of SES in survival from malignant renal tumours in children and young people. We did not detect a significant socioeconomic disparity in renal tumour survival. Tumour stage, histological subtype and trial period were each found to be strong predictors of survival and young people had a significantly higher mortality risk compared to children.

The availability of high quality data from the NRYPMDR, including birth certificates, ensures reliability of data on paternal occupation. Furthermore, paternal occupation as an individual-level measure for SES has been shown to be a reliable and valid SES indicator associated with a lower risk of non-differential misclassification compared to area-level measures [28,29]. The availability of detailed clinical information also allows robust analysis of determinants of renal tumour survival.

However, due to the relatively small sample size there was limited statistical power to estimate survival characteristics for young people with a high degree of precision and multivariate Cox regression could only be performed for childhood WT. While we were able to adjust our study findings for a number of important prognostic factors obtained from the registry, residual confounding from other factors such as treatment protocol, relapse rate(s), tumour volume and biomarkers – which were not available – may have led to an over- or under-estimation of survival outcomes. Chance and/or a lack of statistical power cannot be ruled out as possible explanations for some of our study results. The current staging criteria used by UKCCSG/SIOP for childhood renal tumours has also undergone some minor adjustments from earlier staging systems. One such important modification implemented after the MRC-2 trial was the upgrading of patients with regional lymph node involvement from stage II to stage III [30].

While the new staging system was used in the registry from 1980 onwards, the older system would have been used during the period 1968-1979, and the stages on the registry would not have been updated. It is possible that some of the historical WT cases previously classified as stage II prior to 1980 have in fact been misclassified as early stage tumours for the purpose of this study. However, only a small proportion of WT cases diagnosed during the period 1968-1979 were stage II (8/52 of all cases with known stage at diagnosis) and this misclassification effect can be considered negligible. The lack of registry information on fathers' working conditions and level of autonomy meant that paternal occupation could not be classified using the updated NS-SEC occupational classification of SES, which is more salient than the SOC-90 classification in reflecting socioeconomic positions of modern societies [31]. Furthermore, SES was based on paternal occupation at birth but not at a later time point such as time of diagnosis, thus introducing the risk of SES misclassification for some study cases if a change in occupation or paternal role since birth has resulted in a similar change in SES group. The singular use of paternal occupation as a SES proxy also fails to acknowledge the evolving landscape of family structures in the UK through the decades, which has seen the proportion of lone mother households rise from 6% to 22% over the past 30 years. Finally, it is possible that using only paternal occupation as an indicator for SES doesn't fully encapsulate its multidimensional nature and other facets through which it might influence renal tumour survival.

Despite these limitations, the absence of a significant social gradient in renal tumour survival in children and young people is consistent with findings from other population-based studies that have examined the role of SES in survival from various solid tumours in these age groups. Prior studies from the UK, Ireland and Sweden have shown no association between parental SES and central nervous system (CNS) tumour survival in children (0-14 years) using both

individual-level and area-level measures of SES [32,33,34]. Furthermore, a large UK study failed to identify a relationship between material deprivation and survival from most solid tumours in teenagers and young adults aged 13-24 years [35]. Nevertheless, others have reported a significant association between parental SES (measured by educational level) and survival from CNS tumours among children in Switzerland, as well as poorer survival with increasing deprivation for young people in England diagnosed with melanoma and carcinomas' of head, neck and colon [15,36]. The inconsistent findings among such studies may be related to an interaction of underlying differences in cancer symptomatology, patient characteristics, social structures such as accessibility and availability of cancer care services, and the different SES indicators used.

Cancer-specific symptoms may indirectly influence survival via tumour characteristics such as stage at diagnosis. Although a recent study showing that renal tumours in UK children are detected at a more advanced stage and with poorer outcome than in German children, a concurrent clinical audit of all WT cases presenting to three major UK paediatric oncology centres, including the Royal Victory Infirmary (RVI) in Newcastle, showed no evidence of a therapeutic delay once contact with a GP had been made, but rather a system of rapid access to diagnostic investigation and treatment [37]. This implies that the delay in tumour presentation and associated poorer survival among UK children may be linked to factors outside of the cancer care pathway such as issues related to parent recognition of signs/symptoms, or the failure of GPs to detect asymptomatic early stage tumours. While it has been suggested that delays in cancer diagnostic and referral pathways are more likely to occur in countries where general practitioners (GPs) act as gatekeepers to specialist care [38], a systematic review of diagnostic delay in childhood cancers found that renal tumours have a significantly shorter lag-time between symptom recognition and diagnostic confirmation compared to all other

childhood cancers and children with shorter delays are more likely to present with certain cancer warning symptoms such as an abdominal mass, which has a higher probability of prompting urgent health-seeking actions by parents compared to other non-specific cancer symptoms e.g. weight loss and general malaise [39]. Additionally, a Mexican study found no substantial risk of a delayed diagnosis from childhood renal tumours regardless of parental SES [40] with similar findings also reported for abdominal tumours in adults [41]. Therefore, the lack of a significant social gradient in renal tumour survival in this study may be due to the absence of class differences in symptom recognition. The observed predominance of early stage renal tumours in this study regardless of age and histological subtype also supports this hypothesis. It would be of interest to determine whether the survival disparity between the UK and other European countries is rather linked to population differences in renal tumour biology, such as a higher incidence of tumours with genetic mutations that reduce chemotherapy and radiotherapy response rates among UK children, or due to international differences in therapeutic management.

Studies have shown that social gradient in cancer survival could be due to differences in type of treatments offered to patients from different social classes [42] including poorer treatment adherence among patients from lower social classes [43]. Evidence also suggests that when treatment is equal, such as in clinical trials or highly specialized clinics, social class differences in cancer survival disappear [44]. Since all UK children diagnosed with renal tumours have been systematically enrolled in the United Kingdom Children's Cancer Study Group (UKCCSG) and International Society of Pediatric Oncology (SIOP) clinical trials, this could account for the absence of a socioeconomic variation in childhood renal tumour survival. This may not apply to young people (15-24 years) as they were excluded from these trials, universal access to health services free at the point of delivery via the National Health Service (NHS) in

the UK may be a contributing factor for the lack of a clear SES gradient in survival for this age group.

Significantly poorer prognosis observed for young people aged 15-24 years is consistent with evidence that little has changed in renal tumour survival among teenagers and young adults in the UK and northern England [2,14]. A plausible biological basis for this survival disparity is that therapies administered to this age group are often derived from clinical trials conducted in younger children [35] and little translational research has been done to discover potential biological differences in cancers that occur in children versus young people, leading to worse prognosis for renal tumours with age increase [45]. Other explanations for the inverse relationship between survival and age at diagnosis may lie in the latter's association with tumour stage at diagnosis and histological subtype. With risk of late stage disease observed to worsen with increasing age among children with WT, poorer prognosis seen among older age groups may be attributed to higher burden of advanced tumours. Additionally, the majority of young people were diagnosed with NWRTs – a collection of renal neoplasms mostly known to have worse survival outcomes than WT and for which satisfactory treatment protocols are yet to be formulated [46].

Finally, it is acknowledged that no single indicator encapsulates the multidimensionality of SES and that certain indicators are likely to measure only part of its domains [21] and area-level measures might dilute the exposure-outcome relationship as a result of aggregation. This is supported by studies that have shown a disappearance of survival disparities for both childhood and adult cancers when area-level measures of SES were used instead of individual-level measures [35,47]. It is possible that contradictory reports of the relationship between SES

and cancer survival in children and young people are partly due to use of SES indicators that fail to capture both social structure(s) and psychosocial determinants of population health.

In conclusion, this study found no significant social gradient in renal tumour survival among children and young people in northern England. The lack of SES disparities in survival combined with significant temporal improvement in renal tumour survival among children compared to poorer outcome for young people, may reflect systematic recruitment of children into clinical trials that use standardized risk-adapted therapies, suggesting that survival disparity between children and young people observed in our study may be due to differences in therapeutic process. The identification of tumour stage at diagnosis as a strong predictor of survival irrespective of age highlights importance of research to develop appropriate public health interventions that ensure early diagnosis and treatment of renal tumours.

CONFLICT OF INTEREST STATEMENT

There are no conflicts of interest.

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FIGURE LEGENDS

Figure 1 – Kaplan-Meier survival curves showing survival estimates by paternal social class for renal tumours in children and young people resident in northern England, 1968 – 2012.

Figure 2 – Kaplan-Meier survival curves showing survival estimates by tumour stage at diagnosis for renal tumours in children and young people resident in northern England, 1968 – 2012.

Figure 3 – Kaplan-Meier survival curves showing survival estimates by Tumour stage at diagnosis for Wilms' tumour in children (0-14 years) resident in northern England, 1968 – 2012.

SUPPLEMENTAL TABLE LEGENDS

SUPPLEMENTAL TABLE S1 – Sociodemographic and clinicopathologic characteristics of all cases of Wilms' tumour in children (0-14 years) resident in northern England, 1968 – 2012.

SUPPLEMENTAL TABLE S2 – Sociodemographic characteristics by tumour stage of diagnosis and the relative risk of presenting with late stage disease for all cases of Wilms' tumour in children (0-14 years) resident in northern England, 1968 – 2012.

SUPPLEMENTAL TABLE S3 **–** One-, Five-, and Ten-year crude survival rates (95% confidence intervals) according to sociodemographic and clinicopathological factors for Wilms' tumour in children (0-14 years) resident in northern England, 1968 – 2012.

TABLE 1 – Sociodemographic and clinicopathologic characteristics of all cases of renal tumours in children and young people resident in northern England, 1968 – 2012.

Variable	N (% of Total)
Age at diagnosis (years)	
0 - 1	58 (28)
2 - 4	90 (43)
5 - 14	42 (20)
15 - 24	19 (9)
Paternal Social Class	
I/II	54 (26)
IIIN/M	89 (43)
IV/V	40 (19)
Unknown	26 (12)
Calendar Period	
1968 – 1977	50 (24)
1978 – 1987	42 (20)
1988 – 1997	56 (27)
1998 – 2007	37 (18)
2008 – 2012	24 (12)
Tumour stage	
Early stage tumour (stage I-II)	89 (43)
Late stage tumour (stage III-IV)	71 (34)
Bilateral disease (stage V)	14 (7)
Missing data	35 (17)
Histological subtype	
Wilms' Tumour	178 (85)
Non-Wilms renal tumours	31 (15)
• Congenital mesoblastic nephroma	5 (2)
• CCSK	2 (1)
• RTK	2 (1)
• pPNET	2 (1)
• RCC	20 (10)
Survival status at end of follow up period	
Dead	59 (28)
Survived	150 (72)
Total	209

TABLE 2 **–** One-, Five-, and Ten-year crude survival rates (95% confidence intervals) and crude hazard ratios with corresponding p-values according to sociodemographic and clinicopathological factors for renal tumours in children and young people resident in northern England, 1968 – 2012.

Covariate	1-year survival	5-year survival	10-year survival	Crude Hazard Ratio (95% CI)	*P*-value
All cases					
Study population (total)	86 (80 – 90)	74 (67 – 79)	73 (67 – 79)	n/a	n/a
Sex					
Female	87 (80 – 92)	75 (66 – 82)	75 (66 – 82)	1.00	0.359
Male	84 (75 – 90)	72 (62 – 80)	71 (60 – 79)	1.27 (0.76 – 2.12)	
Age at diagnosis (years)					
0 – 1	88 (76 – 94)	83 (70 – 90)	83 (70 – 90)	1.00	n/a
2 – 4	87 (78 – 92)	77 (67 – 84)	75 (65 – 83)	1.56 (0.75 – 3.26)	0.240
5 – 14	88 (74 – 95)	69 (53 – 81)	69 (53 – 81)	1.98 (0.88 – 4.45)	0.100
15 – 24	68 (43 – 84)	42 (20 – 63)	42 (20 – 63)	4.43 (1.88 –10.45)	0.001
Paternal Social Class					
I/II	87 (75 – 94)	74 (60 – 84)	72 (58 – 82)	1.00	n/a
IIIN/M	84 (75 – 90)	73 (62 – 81)	73 (62 – 81)	1.18 (0.60 – 2.30)	0.64
IV/V	85 (70 – 93)	75 (59 – 86)	75 (59 – 86)	1.17 (0.53 – 2.62)	0.70
Calendar period					
1968 – 1977	78 (65 – 87)	63 (48 – 74)	61 (46 – 73)	1.00	n/a
1978 – 1987	78 (62 – 88)	68 (52 – 80)	68 (52 – 80)	0.89 (0.46 – 1.74)	0.74
1988 – 1997	86 (74 – 93)	71 (58 – 81)	71 (58 – 81)	0.66 (0.34 – 1.28)	0.22
1998 – 2007	97 (82 – 100)	89 (74 – 96)	89 (74 – 96)	0.23 (0.08 – 0.68)	0.008
2008 – 2012	96 (74 – 99)	88 (66 – 96)	88 (66 – 96)	0.28 (0.08 – 0.93)	0.04
Tumour stage					
Early stage tumour (I-II)	91 (82 – 95)	85 (76 – 91)	84 (75 – 90)	1.00	n/a
Late stage tumour (III-IV)	82 (71 – 89)	56 (44 – 67)	56 (44 – 67)	3.47 (1.85 – 6.52)	<0.001
Bilateral disease (V)	71 (41 – 88)	64 (34 – 83)	64 (34 – 83)	2.86 (1.03 – 7.97)	0.04
Histological subtype					
Wilms' Tumour	88 (83 – 92)	76 (69 – 82)	76 (69 – 81)	1.00	n/a
Non-Wilms renal tumour	71 (52 – 84)	58 (39 – 73)	58 (39 – 73)	2.02 (1.09 – 2.17)	0.026

Abbreviations: n/a – not applicable
CI – Confidence Interval

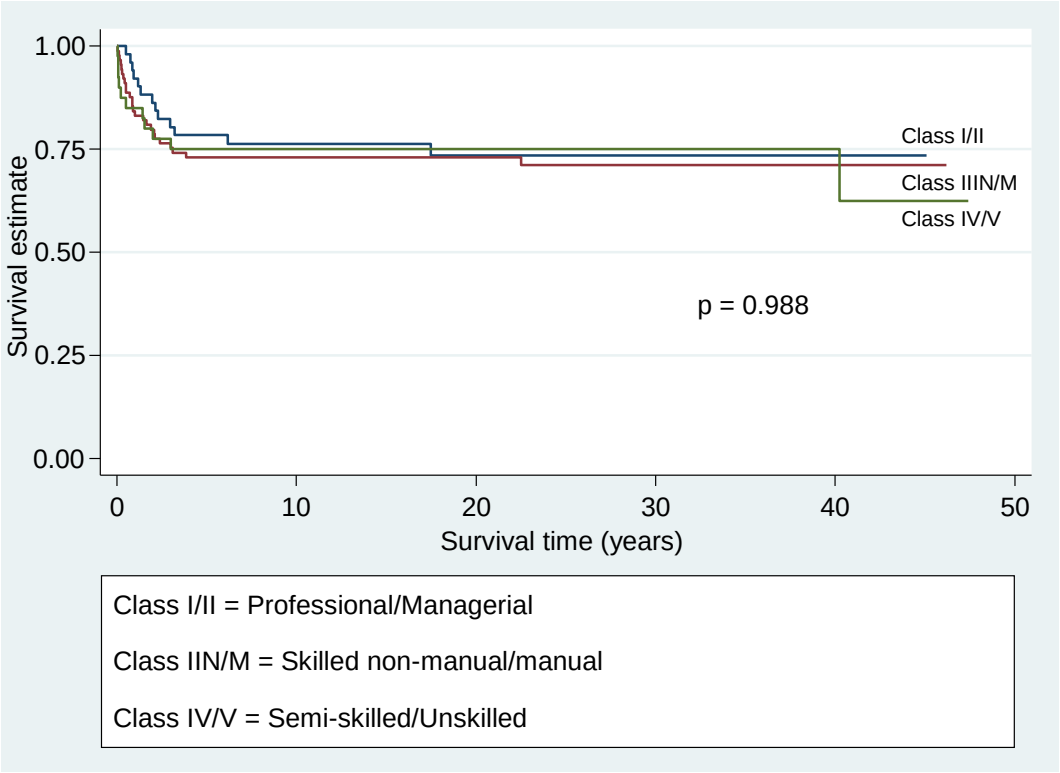
NB: Data represent survival rates in percentages (95% confidence interval) unless stated otherwise

TABLE 3 – Crude and adjusted hazard ratios (95% Confidence Interval) by demographic and clinicopathological factors for WT in children aged 0-14 years in northern England, 1968 – 2012.

Covariate	Crude Hazard Ratio (95% CI)	*P*-value	Adjusted Hazard Ratio* (95% CI)	*P*-value
Sex				
Female	1.00	0.180	1.00	0.629
Male	1.54 (0.82 – 2.89)		1.22 (0.78 – 2.85)	
Age at diagnosis				
0 – 1	1.00	n/a	1.00	n/a
2 – 4	1.57 (0.67 – 3.69)	0.303	0.87 (0.48 – 2.28)	0.771
5 – 14	1.98 (0.77 – 5.10)	0.158	0.98 (0.35 – 2.78)	0.972
Paternal Social Class				
I/II	1.00	n/a	1.00	n/a
IIIN/M	1.20 (0.53 – 2.72)	0.663	1.12 (0.48 – 2.59)	0.791
IV/V	1.37 (0.53 – 3.55)	0.520	1.47 (0.55 – 3.91)	0.443
Tumour Stage				
Early stage (I-II)	1.00	<0.001	1	<0.001
Late stage (III-IV)	6.35 (2.79-14.44)		6.37 (2.60 - 15.59)	
Trial Period				
MRC 1 & 2 (1968-1979)	1.00	n/a	1.00	n/a
UKW1-UKW3 (1980-2001)	0.39 (0.20-0.77)	0.007	0.36 (0.17 - 0.78)	0.009
SIOP 2001 (2002-2012)	0.22 (0.07-0.76)	0.016	0.13 (0.02 - 0.99)	0.049
Calendar Period				
1968 – 1977	1.00	n/a		
1978 – 1987	0.69 (0.31 – 1.56)	0.377		
1988 – 1997	0.38 (0.16 – 0.92)	0.031	–	–
1198 – 2007	0.38 (0.13 – 1.14)	0.086		
2008 – 2012	0.14 (0.02-1.05)	0.056		

Abbreviations: n/a – not applicable
CI – Confidence Interval
*****Adjusted for sex, age at diagnosis, social class, tumour stage and trial period (calendar period not included)

FIGURE 1 – Kaplan-Meier survival curves showing survival estimates by paternal social class for renal tumours in children and young people resident in northern England, 1968 – 2012.



Class I/II = Professional/Managerial

Class IIN/M = Skilled non-manual/manual

Class IV/V = Semi-skilled/Unskilled

FIGURE 2 – Kaplan-Meier survival curves showing survival estimates by tumour stage at diagnosis for renal tumours in children and young people resident in northern England, 1968 – 2012.

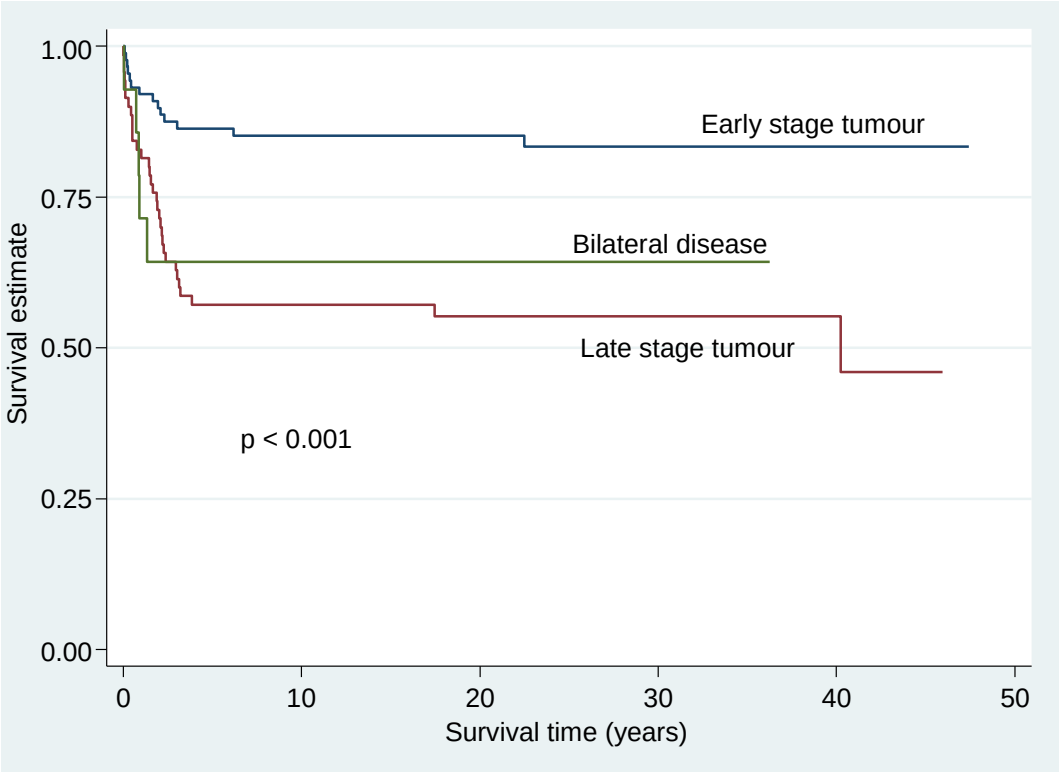
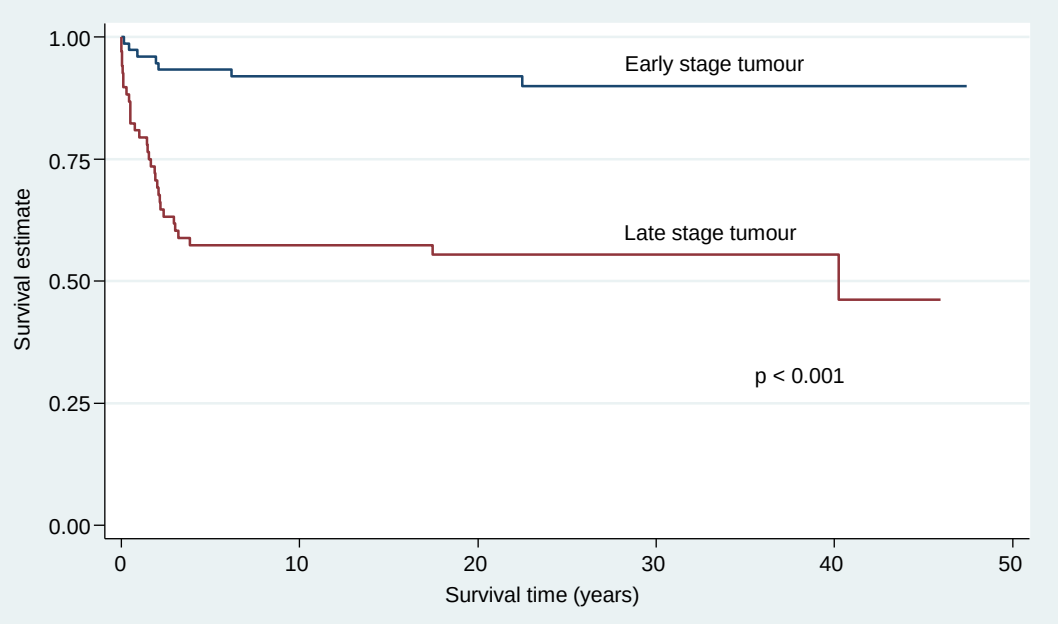


FIGURE 3 – Kaplan-Meier survival curves showing survival estimates by Tumour stage at diagnosis for Wilms' tumour in children (0-14 years) resident in northern England, 1968 – 2012.



SUPPLEMENTAL TABLE S1 – Sociodemographic and clinicopathologic characteristics of all cases of Wilms' tumour in children (0-14 years) resident in northern England, 1968 – 2012.

Variable	**N (% of Total)**
Age at diagnosis (years)	
0 - 1	43 (26)
2 - 4	84 (52)
5 - 14	35 (22)
Paternal Social Class	
I/II	44 (27)
IIIN/M	68 (42)
IV/V	31 (19)
Unknown	19 (12)
Calendar Period	
1968 – 1977	46 (28)
1978 – 1987	31 (19)
1988 – 1997	43 (26)
1998 – 2007	25 (16)
2008 – 2012	17 (11)
Tumour stage	
Early stage tumour (I-II)	75 (46)
Late stage tumour (III-IV)	68 (42)
Missing data	19 (12)
Survival status at end of follow up period	
Dead	39 (24)
Survived*	123 (76)
Total	162
***Includes censored cases**	

SUPPLEMENTAL TABLE S2 – Sociodemographic characteristics by tumour stage of diagnosis and the relative risk of presenting with late stage disease for all cases of Wilms' tumour in children (0-14 years) resident in northern England, 1968 – 2012.

Covariate	Early stage tumour (% of n)	Late stage tumour (% of n)	Relative Risk (95% CI)	*P*-value
Sex				
Female	43 (56)	36 (53)	1.00	0.873†
Male	32 (44)	32 (47)	1.10 (0.77 – 1.59)	
Age at diagnosis (years)				
0 – 1	29 (78)	8 (22)	1.00	
2 – 4	33 (45)	40 (55)	1.57 (1.20 – 2.04)	0.001‡
5 – 14	13 (39)	20 (61)	2.31 (1.40 – 3.79)	
Paternal Social Class				
I/II	23 (34)	16 (28)	1.00	
IIIN/M	30 (45)	27 (47)	1.11 (0.80 – 1.55)	0.736†
IV/V	14 (21)	14 (26)	1.23 (0.70 – 2.18)	

Keys: n - number of cases per tumour stage category

† - Pearson's χ^2 test

‡ - χ^2 test for trend

NB: Cases with missing data not included

Level of significance (α) is < 0.05 for all statistical tests

SUPPLEMENTAL TABLE S3 **–** One-, Five-, and Ten-year crude survival rates (95% confidence intervals) according to sociodemographic and clinicopathological factors for Wilms' tumour in children (0-14 years) resident in northern England, 1968 – 2012.

Covariate	1-year survival	5-year survival	10-year survival
Study subset			
All WT cases	90 (84 – 93)	79 (71 – 84)	78 (71 – 84)
Sex			
Female	93 (86 – 97)	81 (71 – 88)	81 (71 – 88)
Male	85 (75 – 92)	76 (64 – 84)	74 (63 – 83)
Age at diagnosis (years)			
0 – 1	88 (74 – 95)	84 (64 – 92)	84 (64 – 92)
2 – 4	89 (90 – 94)	79 (68 – 86)	77 (67 – 85)
5 – 14	92 (76 – 97)	72 (54 – 84)	72 (54 – 84)
Paternal Social Class			
I/II	93 (80 – 98)	84 (70 – 92)	82 (67 – 90)
IIIN/M	90 (80 – 95)	78 (66 – 86)	78 (66 – 86)
IV/V	87 (69 – 95)	77 (58 – 89)	77 (58 – 89)
Calendar period			
1968 – 1977	80 (66 – 89)	65 (50 – 77)	63 (48 – 75)
1978 – 1987	87 (69 – 95)	77 (58 – 89)	77 (58 – 89)
1988 – 1997	93 (80 -98)	84 (69 – 92)	84 (69 – 92)
1998 – 2007	96 (76 – 100)	85 (64 – 94)	85 (64 – 94)
2008 – 2012	94 (65 – 99)	94 (65 – 99)	-
Tumour stage			
Early stage tumour (I-II)	96 (88 – 99)	93 (85 – 97)	92 (83 – 96)
Late stage tumour (III-IV)	81 (69 – 98)	57 (45 – 68)	57 (45 – 68)

Abbreviations: n/a – not applicable
CI – Confidence Interval
WT – Wilms' Tumour

NB: Data represent survival rates in percentages (95% confidence interval) unless stated otherwise